

THE

FAMILY GENETIC SOURCEBOOK

*Helps you to anticipate and understand
genetic diseases and disorders*

A-Z catalog of traits and disorders

*Concise coverage of basic concepts and
history of genetics*

Benjamin A. Pierce

THE FAMILY GENETIC SOURCEBOOK

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To Marlene, Sarah, and Michael



PREFACE

During the past decade, incredible advances in the study of genetics have transformed our understanding of human heredity. Scientists have identified scores of new genes, genes that influence our appearance, our biochemistry, our health, and even our behavior. Powerful new techniques in molecular genetics are altering the way biologists study heredity and are providing detailed information about the mechanisms of gene action. Perhaps the most important theme to emerge from this work is that genes are central to who and what we are.

In spite of recent advances in the study of genetics and the growing importance of human heredity, the average person knows little about the nature of genes or how they work. This lack of understanding is not because people are disinterested in their heredity. On the contrary, as a professional geneticist I am continually approached by parents, students, and friends who ask: "How is red hair inherited?" or "My father has heart disease; am I likely to inherit it?" or "Is obesity genetic?" Geneticists have detailed answers to many of these questions; yet, little of the information has been available to the average person. My goal in writing this book is to provide such information to the layperson in a direct, clear, and nontechnical style.

The Family Genetic Sourcebook is divided into two parts. The first half consists of seven chapters that provide an introduction to the principles of heredity. Chapter 1 discusses the importance of heredity and provides a brief history of the study of genetics; I emphasize a number of recent advances that have revolutionized the field of human genetics. Chapter 2 focuses on basic concepts: What a gene is, how genes determine our traits, how genetic information is encoded, the structure of a chromosome, and how chromosomes are inherited. Chapter 3 explains the inheritance of simple genetic traits, and Chapter 4 discusses the inheritance of more complicated multifactorial traits. Chapter 5 touches on chromosome disorders. Chapter 6 explains genetic counseling, prenatal diagnosis, and treatment of genetic diseases. Chapter 7 contains detailed instructions for charting your own family history.

The second part of the book, entitled "The Catalog of Genetic Traits" is an alphabetical listing of over 100 human traits, diseases, and disorders

that have a genetic basis. Each entry in the catalog contains a brief description of the trait or disease and an explanation of its inheritance. Flipping through the catalog, the reader encounters discussions of how genes influence alcoholism, the genetic basis of diabetes, and how reading disabilities are inherited. The genetics of height, weight, eye color, hair color, intelligence, and many other human traits are explained. Cross-listings and references to relevant sections in the introductory chapters facilitate easy use of the catalog and enable the reader to acquire an understanding of the principles of human heredity.

The Family Genetic Sourcebook is not a book written primarily for physicians or geneticists; however, I think many physicians and geneticists will find it a useful guide for explaining inheritance and a handy reference to human genetic traits. Rather, my intended audience consists of people with little or no formal training in genetics but with an interest in heredity; this will include parents and prospective parents, teachers, social workers, nurses, biology students, and any reader with an interest in their own heredity. I have tried to keep that audience firmly in mind as I explain how heredity works and how human traits are inherited. I have attempted to clarify complex processes and, wherever possible, to use nontechnical terms. But I have avoided simplification. Too often, human inheritance is explained to the layperson only in terms of simple patterns of inheritance—autosomal dominant, autosomal recessive, or X-linked inheritance. Thus, many people believe (incorrectly) that blue eyes is a simple recessive trait or that left-handedness is inherited in a straightforward fashion. Unfortunately, the inheritance of most human traits is more complex. Even the layperson must master the concepts of penetrance, genetic heterogeneity, and multifactorial interactions to understand his or her own inheritance. One of the themes that I hope the book conveys is that many human traits are genetic, but few have a simple genetic basis.

The book should not be used as a “do-it-yourself” guide to genetic counseling. I have attempted to help the reader understand how inheritance works and to appreciate that many common traits and diseases are influenced by genes. Where possible, I have attempted to give a brief account of the genetics of human traits, and some idea of the chances of passing the traits on. However, I have repeatedly emphasized the complexities of many genetic diseases and the importance of seeking counsel from a physician or genetic counselor when such a disorder runs in the family. At the back of the book I have provided an extensive list of genetic centers where genetic counseling and prenatal diagnosis are available.

The Family Genetic Sourcebook can be a valuable companion for genetic counseling, but should not serve as a substitute for it.

"The Catalog of Genetic Traits" is far from a complete listing of all human traits and diseases with a genetic basis; thousands of human traits and disorders are influenced by genes, but only a few could be included. I have omitted many classical genetic diseases because they are rare and will be of little interest to the average reader. I have tried to discuss traits that many people have questions about and traits that I think the reader will find interesting. In addition, my hope is that the traits included will convey to the reader a sense of the diversity of human traits that are influenced by genes. There are hundreds of other genetic traits that I would have liked to discuss, but limitations of space prevented their inclusion.

This book has been made possible by the contributions of numerous people. Ray Canham and Jeffry Mitton stimulated my initial interest in heredity and helped shape my professional development as a population geneticist. Tom Hanks and members of the Baylor Scholarly Writing Workshop assisted in the improvement of my writing skills. Sharon Conry, George Hudock, Ricki Lewis, Amanda Pierce, J. Rush Pierce Sr., and J. Rush Pierce Jr. read initial drafts of the book and made valuable suggestions on content, organization, style, and clarity. J. Rush Pierce Sr. and J. Rush Pierce Jr. shared with me their medical expertise concerning many of the diseases included in the catalog. Marlene Tyrrell carefully edited the entire book, greatly improving its readability. Ted Scheffler, David Sobel, Nancy Woodruff at John Wiley & Sons, and Bob Cooper at Spectrum Publisher Services expertly guided the book through its inception, development, and publication. Finally, I wish to thank my family—Marlene, Sarah, and Michael—for their encouragement, their patience, their unending support.

Benjamin A. Pierce



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Chapter 1

GENES, HEREDITY, AND HUMAN AFFAIRS

Albinism in the Hopi Indians

On the edge of the Painted Desert in northern Arizona rises a large flat-topped mountain called Black Mesa, the home of the Hopi Indian tribe. Fingerlike projections of the mesa extend down into the surrounding desert, and perched alongside and on top of the barren mesa rocks are 11 Hopi villages. In spite of their small size and isolation, many of the villages are quite old. One village, Oraibi, was established in 1150 A.D. and is one of the oldest continually occupied settlements in North America.

Ales Hrdlička, a physician and anthropologist, visited the Hopi villages of Black Mesa in 1900 and made a startling observation: Among the normally dark-skinned inhabitants of the villages were 11 white people—not fair-skinned Caucasians, but white Hopis. These peculiar Indians were albinos; they suffered from a disorder that prevents the formation of pigment in the skin, hair, and eyes. Albinism is a genetic disorder, a disease caused by a defective gene. Genes are the fundamental units of heredity, consisting of pieces of chemical information that determine our traits, and they pass from parent to offspring at the moment of conception. No one knows exactly how many genes we possess, but a rough estimate is around 100,000. Among this vast inventory of genetic information is a gene that codes for pigmentation. In an albino, that gene is defective.

Albinism actually comes in several varieties. In the most severe form, pigment is never produced. Albinos with this condition possess completely white skin and hair, lacking even a trace of pigment. In another type, the genetic defect greatly reduces pigmentation, but slight coloring of the skin, hair, and eyes frequently occurs with age; this less severe form of albinism is the type found among the Hopis. Besides influencing pigmentation, the gene that causes albinism produces other effects. For example, nystagmus, a condition that involves jerky movements of the eyeballs, is common, and many albinos are legally blind. The skin of an

albino is also extremely sensitive to sunlight, so sunburning is a constant problem, and skin cancer occurs frequently.

Albinism is not unique to the Hopis. In fact, albinos occur in all human races, and human albinos are mentioned in ancient writings. The Hopis are remarkable, not because albinos are present among members of the tribe, but because this genetic trait occurs in incredibly high frequency among the inhabitants of certain Hopi villages. In 1900, when Hrdlička visited Black Mesa, the frequency of albinos was 1 out of every 182 Hopis. Almost 70 years later, in 1969, 26 albinos were found on the reservation, giving a frequency of 1 in 231 inhabitants. The incidence of albinism among other human groups is much lower: only about 1/40,000 in North American whites, or 200 times less frequent than in the Hopi Indians. The frequency in other races varies somewhat, but albinism is usually quite rare. Why is this genetic trait so much more common in the Hopis than among other people? Studies carried out in the 1960s by Charles Woolf and Frank Dukepoo of Arizona State University suggest that the answer to this question lies in the unique place that albinos occupy in the Hopi culture and heritage.

Unlike people with genetic defects in many societies, albinos have always been given high regard in the Hopi community. Traditionally, the tribe completely accepted the albinos and considered them to be smart, clean, and pretty. Many Hopis associated the whiteness of an albino with purity. Albinos performed in Hopi ceremonies and, in the past, assumed positions of leadership as chiefs and priests. They were seen as a special part of the Hopi heritage—the presence of many albinos in one's village was regarded as a desirable sign of racial purity.

In the hot arid environment of the Southwest, sensitivity to the sun can be an incapacitating trait, and albinos are extremely vulnerable to sunburning. However, albinos in the Hopi community received special consideration. The Hopis have farmed for centuries, working fields of corn and vegetables below the mesa. Traditionally, all the Hopi men and boys would leave the villages each day and go to the fields to work, returning only after sundown. Because of their sensitivity to the sun, male albinos were apparently excused from this labor. Instead of working the fields, they remained behind with the women of the village, performing tasks such as weaving, cooking, and cleaning. Woolf and Dukepoo suggest that by remaining in the village during the day, albino men had more opportunities for sexual activity with the women of the tribe. Perhaps in this way the genes for albinism were spread throughout the village and reached such a high frequency. We cannot be certain that this is the sole reason that albinos are so common among the Hopi people, but the facts



Figure 1.1. Three Hopi Indian girls, taken about 1900. The girl in the center is an albino. (Field Museum of Natural History [Neg# 118], Chicago.)

are consistent with this explanation. Even if other factors are involved, there is little doubt that the special status accorded the albino in Hopi culture has contributed to the high frequency of albino genes in that culture.

How Genes Influence Our Lives

Albinism in the Hopi Indians illustrates how possessing a single gene can profoundly affect one's life. In the Hopi culture, an albino was set apart, given special status, and provided with a different role in society—all

because of a single genetic difference. Of course, most of us are not albinos. Nevertheless, the genes we do possess mark us in ways that may have just as great an impact. Genes determine our height, our weight, and our looks—all of which influence how others react to us and how we view ourselves. Genes influence our physical strength, and they affect our susceptibility to many diseases and psychiatric disorders. They even play a role in shaping our intelligence.

To be sure, genes don't completely run our lives; we are not simply robots blindly following the programmed instructions of our genes. There is little doubt that genes do point us in certain directions, however, making us more susceptible to some influences and less susceptible to others. Consider hereditary predisposition to alcoholism. A large number of studies demonstrate that genes influence addiction to alcohol, and alcoholism tends to run in families. If your father was an alcoholic, you are more likely to become an alcoholic yourself, even if you were adopted into a foster home at birth and never met your father. In fact, sons of hospitalized alcoholic fathers are four times more likely to become alcoholic than those without an alcoholic father, even when both groups are reared by nonalcoholic foster parents. So genes affect alcoholism, but there is no gene that forces anyone to drink. Genes may make us susceptible to alcohol abuse; they may increase or decrease our "risk" of becoming an alcoholic. Our free will is also involved, however, and the vast majority of sons and daughters of alcoholic fathers never become alcoholics themselves. We don't yet know *how* genes affect our susceptibility to alcoholism. Perhaps the genes promote certain personality types, and these personalities are more likely to become dependent on alcohol. Perhaps genes influence how we metabolize alcohol, which in turn affects our tendency to overdrink. It doesn't really matter how genes do this, although the question is certainly interesting; more important is recognizing that our susceptibility to alcoholism is influenced by our genes.

Heredity and Health

One way genes affect us is by influencing our health. Most of us will personally suffer from several major diseases during our lifetime, and disease constantly touches those around us. However, few of us think

much about genetic diseases. We may know someone who has a child with Down syndrome or a child with a birth defect, but, in general, we think of genetic diseases as rare disorders that affect other people. To some extent this notion is true. Many genetic diseases are rare, particularly those with devastating effects in newborns and children. Down syndrome, the most common of the chromosomal disorders, occurs with a frequency of only about 1 in 800 births (though the frequency in older mothers is considerably higher). Phenylketonuria (PKU) is one of the more common inborn errors of metabolism, and most states require testing of newborns for this genetic disease. Yet the occurrence of PKU is only about 1 in 11,000 births among whites in the United States, and the frequency in blacks is even less. Most of the other classic genetic diseases that we hear about also occur at low frequencies: sickle cell disease arises in 1 out of 600 black births in this country; cystic fibrosis occurs in 1 in 2,000 to 1 in 6,000 white births; hemophilia, or bleeder's disease, appears in 1 out of every 10,000 male births; Tay-Sachs disease has a frequency of only about 1 in 360,000 births in the general population. (But the frequency of these diseases may be much higher in certain ethnic groups; for example, Tay-Sachs disease is about 100 times more common in Ashkenazi Jews, occurring with a frequency of 1 in 3,600 births.)

These classic hereditary diseases, all with a simple genetic basis, are uncommon. Without a family history of the disease, their occurrence in our own children is very unlikely. What is seldom recognized is that many common diseases, including some of the leading causes of death in modern society, are also influenced by our genes. For example, many types of heart disease have a genetic basis. Predispositions to diabetes and to some forms of cancer are inherited. Depression, schizophrenia, and manic-depressive illness are partly genetic. Even obesity, one of the major health problems of our culture, is influenced by genes. The hereditary basis of these diseases is more complicated than that of the classical genetic disorders, and environmental factors are also important. There is little doubt, however, that our susceptibility to these medical problems is affected by our genetic constitution.

Let us consider the genetic history of disease in a typical American family. John and Cathy live in a large midwestern city and are in their middle thirties. John has a degree in business; Cathy is a computer programmer. They have two children: Michael, who is four and Amanda, two. John and Cathy are in good health and both of their children were born with no major medical problems. John and Cathy recently visited their family physician. In discussing their medical histories, the doctor asked whether any genetic diseases occurred in their families. Cathy and John quickly answered no.

However, upon examination of their family histories, we find evidence of a number of genetically influenced diseases and disorders. John has two brothers, both of whom are asthmatics; asthma has a hereditary component. John's father suffers from high blood pressure, and John's uncle died at age 42 of a heart attack following a history of high blood pressure. Several of John's relatives have been hospitalized for depression. Cathy's grandfather developed a hereditary tremor, an uncontrollable shaking of the hands, late in his life, and this trait is already apparent in two of Cathy's brothers. Her father suffers from glaucoma; Cathy's sister and mother both have thyroid diseases. All of these diseases and disorders found in Cathy and John's families are partly hereditary in nature.

John and Cathy might be dismayed by this information, and they might feel that they are particularly unlucky in regard to the genes they carry. However, these are all common medical problems, and we could probably find a similar list of genetic diseases in nearly everyone's family. The point is that all of us carry genes that will affect our health and all of us are susceptible to some genetic diseases. This does not mean that we will develop the diseases or that our children will have them; we simply have a greater chance of getting the diseases than does the average person in the general population. A geneticist would say that John and Cathy, along with their children, are at "greater risk" for developing some of these diseases.

We cannot change the genes we inherit, but we can recognize our susceptibility to certain traits and act to minimize the chance of developing problems. Most of the common genetic diseases—heart disease, cancer, diabetes, alcoholism, psychiatric illnesses—are influenced by environmental factors as well as genes. Although we cannot alter our genetic predisposition, frequently we can change some of the environmental contributors. For example, if you have a long family history of alcoholism, you would do well to limit your alcohol consumption; if high blood pressure runs in your family, you should have regular physical checkups and follow your physician's advice concerning diet and exercise.

Hemophilia in European Royalty

Genes not only shape our personal lives; sometimes they influence the course of history as well. The appearance of hemophilia in the royal

families of Europe illustrates the importance of heredity in the course of human events. Hemophilia, or bleeder's disease, is a rare disorder in which the blood fails to clot—even a bruise can lead to internal bleeding and death. Several forms of hemophilia exist; the one appearing among European royalty was X-linked, which means that the gene causing the disease is located on a particular structure called the X chromosome.

At this point, I need to digress briefly and discuss how we inherit a gene like the one causing hemophilia. The genes we possess come in pairs—each of us actually has two genes for each genetically determined trait. The reason for this is obvious after a moment's reflection: One gene of the pair is inherited from our mother and the other from our father. The two genes that we inherit for a trait may be alike or they may differ, but together they determine the trait. Consider the genes that cause hemophilia. All females have a pair of genes that normally produce a substance required for blood clotting. (Actually a number of gene pairs are involved in different aspects of the clotting process, but for simplicity I will consider only a single pair.) Most women have two normal genes and produce plenty of the blood-clotting factor. Occasionally, a female is born with one gene that codes for the clotting substance and one defective gene that fails to produce the substance (the hemophilia gene). In this case, the woman produces less of the blood-clotting substance, since she has only one functional gene, but that one gene still produces enough of the substance to prevent hemophilia. Thus, the woman with one normal gene and one hemophilia gene will not have hemophilia, but she can still pass the defective gene on to her children; such a person is called a *carrier*. For a female to have hemophilia, she must possess two defective hemophilia genes: one inherited from her mother and one from her father. With two defective genes, no clotting substance is produced, and the woman is a bleeder. When two copies of the gene are required for the trait to be expressed, the gene is said to be *recessive*.

Up to this point, I have purposely confined our discussion of genes and hemophilia to females, because the situation is more complicated in males. The genes are located on structures called *chromosomes*. Most cells of the human body possess 46 chromosomes (notable exceptions are the eggs and sperm), which come in 23 pairs. One of the pairs consists of the sex chromosomes, so called because the sexes are different at this chromosome pair: females have two X-shaped chromosomes, which are appropriately called X chromosomes, and males possess one X chromosome and a smaller chromosome called the Y. Recall that hemophilia is X-linked, meaning that the gene for blood clotting is located on the X chromosome. The X chromosome carries genes that are important in

both males and females, but the inheritance of these genes differs between the sexes, because males and females have different numbers of X chromosomes. All females possess two X chromosomes, one inherited from the mother and one from the father, and thus in females, X-linked genes come in pairs. However, males have only a single X chromosome, which they always inherit from their mother; in order to be male they must inherit their father's Y chromosome. The point I want to emphasize, is that because males have only a single X chromosome, they possess only a single gene for X-linked traits such as hemophilia. If that single gene produces the clotting substance, the male will be free of hemophilia; on the other hand, if the gene is defective, no clotting substance is produced and he will be hemophilic. Although two defective genes must be present for a female to have hemophilia, only a single gene is required in the male; consequently, hemophilia is more common in males than females. In the chapters that follow, I will present a more detailed explanation of how sex is determined and how X-linked traits are inherited. For now, let us return to the history of hemophilia in European royalty.

Most likely, a gene for hemophilia first appeared in the English royal family in 1819, when Victoria Alexandrina was born to the Duke of Kent and the Princess of Saxe-Coburg. Victoria, later Queen of England and ruler of the British Empire for over 60 years, was a carrier of hemophilia; that is, she carried a defective gene for hemophilia, but did not have the disease herself, because she also carried a normal gene for the blood-clotting factor. Victoria bore nine children. One, Leopold, was hemophilic and died at age 31; before his death, he passed on the gene for hemophilia to his daughter. At least two of Victoria's daughters also inherited the gene, but like their mother were unaffected carriers. Through intermarriage of the royal families of Europe, the gene was eventually passed into the royal houses of Germany, Russia, and Spain. In all, ten male descendants of Victoria suffered from hemophilia, and most bled to death at an early age.

The most famous of the royal hemophiliacs was Alexis, born to the Russian Tsar Nicholas II and Alexandra, granddaughter of Queen Victoria. Unknowingly, Alexandra was a carrier of the hemophilia gene. Alexis was her first-born son and male heir to the Russian throne: When he was born in 1904 there was great rejoicing throughout the royal family. Almost immediately, however, Nicholas and Alexandra learned that their son possessed hemophilia—an incurable hereditary disease. The child suffered terribly from the disorder: Minor injuries frequently produced internal hemorrhaging and excruciating pain. His parents for-



Figure 1.2. Tsar Nicholas II and Alexandra of Russia and their children. Alexis, seated beneath Alexandra, suffered from hemophilia, a genetic disease. (The Bettmann Archive.)

bade him to participate in sports and other physical activities that might endanger his life, but scrapes and bruises were inevitable. Alexis went through one crisis after another, and his physicians were frequently helpless to stop his bleeding.

Like most parents with a seriously ill child, Nicholas and Alexandra worried constantly about Alexis and were greatly distressed by his illness and suffering. Alexandra experienced tremendous guilt, and she and Nicholas felt powerless in his bleeding crises. In desperation, they turned to a mystic and monk named Rasputin. Under Rasputin's care, Alexis recovered from several serious bleeding episodes, and Rasputin consequently gained considerable influence over the royal family. At this time, the Russian people revolted, eventually overthrowing the Tsar and ushering in a Marxist state in Russia. Nicholas, Alexandra, and the entire royal family, including Alexis, were executed by the Bolsheviks on July 17, 1918.

Historians have argued that Rasputin's influence on the royal family and the Tsar's distraction with his son's hemophilia paved the way for the Russian Revolution. Perhaps a more peaceful transfer of power might

have taken place had Alexis not been sick. Undoubtedly numerous factors, many of them deeply embedded in the fabric of Russian culture and history, contributed to the uprising of the Russian people. It would be wrong to attribute the Russian Revolution entirely to the presence of one sick child. Nevertheless, a gene for hemophilia, passed down four generations from Queen Victoria to Alexis, deeply affected the lives of Nicholas and Alexandra and played a significant role in the history of world events.

The Historical Roots of Genetics

Heredity in Early Human Cultures

The study of genetics and human heredity is a very young science, being entirely a product of the twentieth century. In fact, the word *gene* did not appear until 1909. Nevertheless, human understanding of heredity and the use of genetic principles extends back more than 10,000 years, to when the first plants and animals were being domesticated for agricultural purposes. The process of domestication required an understanding of heredity. Among the wild plants and animals of nature, many individual differences occurred. Early humans selected those individual plants and animals with desirable traits, and by interbreeding them, they produced offspring with more of the same traits. Continuing this process for many generations, they gradually converted wild plants and animals into the domesticated varieties that made agriculture possible. The success of domestication indicates that early human cultures understood a simple, but important rule of heredity: "like breeds like."

Ancient writings provide evidence that early societies also displayed a keen interest in human heredity and that people recognized the genetic nature of human traits thousands of years ago. Hindu sacred books dating back 2,000 years attribute the characteristics of children primarily to the father, but differences between a son and his father were thought to result from the influence of the mother. These writings also provide rules for choosing a spouse, suggesting that women from a family with undesirable traits should be avoided. The ancient Greeks displayed a thorough knowledge of human heredity, evidence of which permeates their poetic and philosophical literature. The Talmud, a book of Jewish

civil and religious laws based on oral traditions going back thousands of years, describes in some detail the pattern of inheritance for hemophilia. It states that if a woman bears two sons who died of bleeding following circumcision, any additional sons should not be circumcised. Furthermore, the sons of her sisters must not be circumcised, but the sons of her brothers should. This is sound genetic advice based on the X-linked inheritance of hemophilia.

Gregor Mendel, Father of Genetics

Although the notion that traits are inherited has been an essential part of agriculture for thousands of years, and even though ancient civilizations recognized that human characteristics were passed from parent to child, the precise mechanism of inheritance remained unknown until 1865. On February 8 of that year a young Augustinian monk named Gregor Mendel stood before the Natural Science Society of Br \ddot{u} nn (now Brno in Czechoslovakia) and described a series of genetic experiments he had conducted on pea plants grown in the monastery garden. With elegance and simplicity, Mendel outlined his conclusion that traits in pea plants were determined by two factors, one inherited from the female parent and one from the male parent. He explained how these two factors separated when the sex cells (eggs and pollen in plants) were formed, one factor going into each sex cell. When sex cells fused in the process of fertilization, the factor from the pollen united with the factor from the egg, and together they determined the trait of the offspring. Mendel also recognized that chance determined which one of the two factors an offspring inherited from its mother and which one of the two factors it inherited from its father; this role of chance produced distinctive ratios of traits in the offspring.

Mendel spoke again of his work at the next meeting of the society on March 8; following that meeting the secretary of the Natural Science Society asked Mendel to publish the text of his report in the journal of the society's proceedings. The article appeared in print the following year, in 1866. There was considerable interest in his work among those who heard the lectures, but, surprisingly, none of the participants recognized the far-reaching implications of his conclusions. Even more puzzling was the minimal response by the scientific community to the publication of his results. The journal containing his report was sent to 133 other associations of scientists in a number of different countries, and many scientists at that time were conducting experiments on plant breeding.

Nevertheless, no one seemed to notice that Mendel had discovered the key to inheritance.

Mendel continued his genetics experiments for several years, publishing another paper on the subject in 1870. He also carried out a number of other scientific investigations, including horticultural studies of flowers and fruit trees, research with honey bees, and extensive weather observations. In 1868 Mendel was elected abbot of the monastery at Bränn, and his ecclesiastical and administrative duties increased. Several years later, the government increased the tax levied on the monastery property, and, on principle, Mendel refused to pay. The ensuing controversy drained away Mendel's time and health, and he died in his sleep on January 6, 1884.



Figure 1.3. Gregor Mendel, an Augustinian monk, who first discovered the principles of heredity.

Mendel's discovery remained buried in the scientific literature for 35 years. Around the turn of the century, three botanists—Hugo de Vries, a Dutch scientist; Erich von Tschermak, working in Vienna; and Carl Correns, in Tübingen—all began to conduct breeding experiments on plants. Working independently of one another, they repeated experiments of the type that Mendel had carried out 35 years earlier, and they observed the same characteristic ratios in the offspring of their crosses that Mendel had seen. In the process of analyzing and writing up their results, they happened to locate Mendel's 1866 paper on inheritance in pea plants. All three scientists immediately interpreted their own results in terms of Mendel's rules of inheritance and published their results in 1900 with reference to Mendel's work. With the appearance of these three papers in 1900, Mendel's pioneering work in genetics was finally appreciated; today he is generally recognized as the father of genetics.

Archibald Garrod and Genetic Diseases

Following the rediscovery of Mendel's work in 1900, a growing number of biologists began to study heredity. They applied his principles to the inheritance of other organisms, demonstrating that Mendel's rules worked not just for pea plants, but also for mice, fruit flies, chickens, guinea pigs, corn, wheat, and virtually every organism studied. The first person to apply Mendel's principles to human traits was Sir Archibald Garrod, an English physician and biochemist. Garrod had been interested in a peculiar disease called *alkaptonuria*. Individuals with *alkaptonuria* are easily recognized, for their urine turns black upon exposure to air. They also suffer from arthritis, particularly in the spine, but this fact was not recognized in Garrod's time. Garrod became intrigued with the biochemistry of this disorder. What caused the urine of an *alkaptonuric* to turn black? In the course of his studies he noticed that although the disease is rare, several children of a single family were often affected with *alkaptonuria*. Furthermore, the parents of such children were always free from the disease, but frequently were first cousins. Garrod recognized that these observations were consistent with Mendel's theory, and he concluded in 1902 that *alkaptonuria* was a genetic disease.

Later, Garrod observed the same pattern of inheritance in three other human disorders: albinism, which involves a defect in the pigmentation (discussed earlier in this chapter); *cystinuria*, a disorder in which an amino acid called cystine is excreted in the urine, forming crystals and stones in the urinary tract; and *pentosuria*, a harmless metabolic disorder

characterized by excretion of a special sugar in the urine. Garrod went on to suggest that each of these genetic diseases results from a defect in a specific protein. Far ahead of his time, Garrod proposed that each gene codes for a protein, and if a *mutation* (a genetic accident) occurs in the gene, then the protein will be absent and the disease symptoms will result. His idea that genes code for proteins turned out to be correct, and of fundamental importance, but like Mendel's his contribution was not appreciated for many years.

During the first half of the twentieth century, geneticists working on fruit flies, corn, bacteria, and other organisms made great strides in our understanding of genes and heredity. There was considerable interest in the chemical structure of genes, and several studies hinted that a substance called *DNA* was the source of all genetic information. *DNA* is shorthand for deoxyribonucleic acid, a long, elegantly spiraled molecule that is found in all living cells. Although *DNA* appeared to be important to heredity, the physical structure of the *DNA* molecule remained unknown, and so molecular studies of genes were impossible. Over the years, researchers had unearthed a number of important clues about the chemistry of *DNA*, but no one knew exactly how to fit these clues together into a coherent model of *DNA* structure.

The Rise of Molecular Genetics

The science of molecular genetics was born in 1953, when James Watson, a postdoctoral student from the United States, and Francis Crick, a graduate student at Cambridge University in England, unraveled the structure of the *DNA* molecule. Using intuition and creativity, these two scientists put together the available information about the chemistry of *DNA* to produce a molecular model of *DNA* that turned out to be correct in almost all aspects. Watson and Crick showed that *DNA* consisted of a long series of units, called *nucleotides*, linked end to end. The nucleotides came in four types, which are now commonly abbreviated by the letters A, T, G, and C. Watson and Crick proposed that genetic information was encoded within the sequence of nucleotides, with the four types of nucleotides (A, T, G, and C) serving as code letters. Scientists now understood what genetic information looked like at the molecular level, and they began to study the molecular biology of the gene.

At first, advances in molecular genetics occurred at a modest rate. How genetic information was encoded in the *DNA* had yet to be worked out. The processes involved in transmitting the *DNA* to future generations

were unknown, and exactly how the DNA determined a trait was still a mystery. All these problems required new techniques and procedures for manipulating and observing the genes at the molecular level. As new techniques developed, and as more information about the molecular nature of genes accumulated, the pace of new discoveries and insights quickened.

Recombinant DNA

In 1973, 20 years after Watson and Crick's landmark discovery, four scientists working in a laboratory in California conducted an experiment that would fundamentally alter the way genetic research was conducted. Stanley Cohen and Annie Chang, from Stanford University School of Medicine, and Herbert Boyer and R. B. Helling, at the University of California School of Medicine at San Francisco, constructed a novel form of DNA by splicing together two pieces of DNA from different sources. They then implanted this new DNA molecule into a bacterial cell. What they created was a genetically distinct organism that had never before existed. Very quickly, the researchers succeeded in using these same techniques to transfer genes between two different forms of bacteria, and they then transferred genes from a frog into a bacterial cell. They called their new DNA molecules *chimeras*, after the mythological Chimera, which possessed the head of a lion, the body of a goat, and the tail of a serpent.

These techniques for splicing DNA and transferring genes rapidly attained widespread use and have proven to be among the most powerful experimental tools in all of science. Usually called *recombinant DNA* by scientists, but also referred to as *gene cloning*, *gene transfer*, or *genetic engineering*, the methods involve cutting the DNA apart at specific places, modifying and reassembling it, and then placing it back into a cell. In many cases a gene is placed inside bacterial cells, and the bacteria are then used as gene factories to mass-produce a specific fragment of the DNA. With large quantities of a gene, scientists can examine its structure, study the way it functions, and transfer it into cells of other organisms.

The ability to carry out genetic manipulations allowed scientists directly to alter the DNA—in essence, to create artificially designed genes. With this capability, questions in genetic research previously impossible to address could now be studied with relative ease. Within a few years, information about the nature of genetic information was pouring forth at

an incredible rate, and the new findings changed some of our most fundamental concepts about genes and how they work. In addition to using these techniques in genetic research, biologists began to apply them to problems in other fields of biology, such as development, evolution, physiology, and neurobiology. In these areas, recombinant DNA has also yielded spectacular advances; the new technology is currently revolutionizing the entire field of biology.

Recombinant DNA technology also promises to be a major economic force. In 1976 the first biotechnology company, Genentech, was formed to develop commercial applications from recombinant DNA methods; now, 350 to 400 biotech companies are in business. Many pharmaceutical, oil, chemical, agricultural, and food-processing companies are currently using recombinant DNA techniques to develop new products, such as crops that produce their own pesticides, bacteria that consume toxic wastes, and vaccines against malaria. Several products produced by these methods are already on the market, and sales in the field are projected to exceed one billion dollars annually by 1990. John Naisbitt, author of *Megatrends* (a best-selling book on future economic and social trends), predicts that biotechnology will be to the coming twenty years what electronics has been for the past twenty years.

A Revolution in Human Genetics

While developments in molecular genetics and genetic engineering have been attracting public attention, a quieter but perhaps more significant transformation has been taking place in the science of human heredity. New techniques in molecular genetics have certainly contributed much to this revolution, yet important developments in several other areas have also made significant contributions. Diagnostic procedures, such as ultrasound technology, biochemical assays, hormone tests, and chorionic villus sampling, have greatly improved our ability to detect genetic diseases. Microscopic study of chromosomes has now reached a fine art, and computer-driven machines are used to quickly analyze large numbers of chromosomes. Powerful computer programs have been developed that analyze patterns of inheritance in families, a technique called *complex segregation analysis*.

Let's consider complex segregation analysis. This technique has recently been used to study the inheritance of a number of diseases and disorders. For example, leprosy is an age-old disease caused by a bacterium. The disease was well known in biblical times and even today it

affects about 13 million people worldwide. In its severest form, leprosy can produce paralysis, disfigurement, and blindness, but people infected with leprosy exhibit a variety of responses. Some people have no obvious symptoms, some are mildly affected, and others are grossly disfigured by the disease. Physicians have noticed that members of some families are vulnerable to leprosy infection, whereas members of other families appear to be relatively immune. This observation suggests that genes play some role in susceptibility to the leprosy bacteria. However, no specific pattern of inheritance is obvious. Geneticists have recently applied complex segregation analysis to leprosy in an attempt to determine if genes are involved in the disease. One such study was conducted on 27 families from the island of Desirade. This small Caribbean island has one of the highest frequencies of leprosy in the world. For over 200 years, all people with leprosy from a number of surrounding islands were deported to Desirade. When the leper colony was closed in 1959, most of the leprosy patients remained on the island. In 1984, 53 islanders with leprosy were examined, and their family histories were recorded. Complex segregation analysis using computers was then applied to the information. The results indicated that genes are important to leprosy infection; susceptibility to the disease is probably controlled by a single gene. Although genes may influence one's susceptibility to leprosy, leprosy should not be considered a genetic disease—it is caused by bacteria, and one cannot contract leprosy unless exposed to the bacteria.

The technique of complex segregation analysis, which was impossible before the advent of modern computers, is now providing valuable insight into the genetic basis of breast cancer, colon cancer, heart disease, birth defects, depression, and numerous other diseases and disorders.

Complex segregation analysis is just one of many new developments that are rapidly expanding our knowledge of human heredity. Advances in molecular genetics are also being applied to problems in human genetics. Along with numerous other applications, molecular techniques are helping to determine where genes are located on the chromosomes; using this approach a number of genes for important hereditary diseases have been located within the past five years. Genes for muscular dystrophy, neurofibromatosis, chronic granulomatous disease, Huntington's disease, polycystic kidney disease, cystic fibrosis, and Alzheimer's disease have now been mapped to specific chromosomes. Finding the particular chromosome where a gene resides is significant, because once the chromosomal location of a disease-causing gene has been established, geneticists can narrow their focus, find the gene itself, and isolate it. The gene can then be transferred to bacterial cells with recombinant DNA

techniques and produced in large quantities, allowing the gene to be studied in detail. Information from such studies may eventually tell us how the symptoms of the disease arise and may suggest strategies for treatment.

Recent developments in the study of Duchenne muscular dystrophy illustrate the power of this approach. Duchenne muscular dystrophy is one of the most common of the inherited muscle disorders; it has devastating effects on the patient and his family. Like hemophilia, the disease is X-linked and therefore occurs mostly in males. A child with this disorder appears completely normal at birth; the subtle symptoms of the disease are not noticeable until about age three. At first, a boy with Duchenne muscular dystrophy may have difficulty getting up from the floor or climbing stairs. Stumbling becomes more and more frequent. The child experiences muscle weakness that gets progressively worse, and eventually he loses the ability to walk. Most boys with Duchenne muscular dystrophy die before reaching their twentieth birthday.

Duchenne muscular dystrophy was first described in 1852, but until recently the biochemical cause of the disease remained a mystery. Even today no cure or even therapy for slowing the disease is available. Within the last three years, however, rapid progress has resulted from the application of molecular techniques to the study of this disease. The gene's location on the X chromosome was recognized a number of years ago from its distinctive pattern of X-linked inheritance. Assigning it to a precise place on the X chromosome, however, was not accomplished until 1983, when molecular techniques were combined with family studies of the disease. Three years later, in 1986, DNA from the muscular dystrophy gene was isolated and cloned in a bacterial cell. With the cloned gene, scientists were able to compare the DNA of patients with Duchenne muscular dystrophy with that of normal individuals. This research quickly indicated that the muscular dystrophy gene consists of a defective piece of DNA; the corresponding DNA from a normal individual produces a protein essential for proper muscle development. Those with Duchenne muscular dystrophy have a defective copy of this normal gene and therefore fail to produce the essential protein. This much was clear from examination of the DNA itself, but the essential protein involved in the disease was still unknown. Only five months later, however, biologists had discovered the protein and named it *dystrophin*.

With dystrophin in hand, a number of important facts about Duchenne muscular dystrophy became apparent. Normal individuals have dystrophin, but the protein is absent in those with Duchenne muscular dystrophy. Even in normal individuals, dystrophin is present only in tiny